



Attorney Docket No. 9052-67

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Colin Brown

Serial No.: 09/700,057

Filed: February 5, 2001

For: *SURGICAL COMPOSITIONS AND METHODS FOR USING THE SAME*

Confirmation No. 1282

Examiner: Everett White

Group Art Unit: 1623

Commissioner for Patents
Post Office Box 1450
Alexandria, Virginia 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132
OF ELIZABETH PEERS, MA, PhD

Sir:

I, Elizabeth Peers, MA, PhD, do hereby declare and say as follows:

1. I received an MA in Natural Sciences (Pharmacology) class I from Newnham College at the University of Cambridge in Cambridge, England and a PhD in Physiological Biochemistry from Imperial College at the University of London in London, England. I am currently the Director of Clinical and Preclinical Development at Innovata Ltd in the United Kingdom, and I am a representative of the assignee of the above-identified patent application. A *curriculum vitae* is attached herewith at Tab 1.

2. I have reviewed the Office Action, dated November 22, 2006 issued in association with the above-identified patent application and am familiar with the contents thereof. I have also reviewed Dobbie, "Separation of Peritoneal Surfaces Through the Maintenance of an Artificial Ascites as a Preventative of Peritoneal Adhesions." Abstract, 4th Peritoneum and Peritoneal Access Meeting, September 16-19, 1997 and U.S. Patent No. 4,886,789 to Milner, both of which are cited in the Office Action.

3. Some of my research interests relate to the study of renal disease, pain, drug delivery, post-surgical adhesions and prostate cancer, for drugs and devices. I am further involved in developing such drugs and devices from concept through preclinical and formulation development and clinical trials with the intent of obtaining regulatory approval in Europe, the United States and other territories.

4. Adhesions are the single greatest complication of surgery. Young et al. *Fertility and Sterility* 84: 1450-1456 (2005). Ninety-three percent of patients undergoing abdominal surgery are affected by adhesions. Menzies and Ellis. *Annals Royal College of Surgeons of England* 72:60-63 (1990). Adhesions can result in infertility, bowel obstruction and chronic pelvic pain, and thus, adhesions may have a significant impact on health-care costs, time and quality of life. The present invention is directed to methods of reducing the incidence of post-operative adhesions.

5. The cited references are directed to methods including peritoneal dialysis. Peritoneal dialysis is a process employed when the kidneys are irreversibly damaged by disease and can no longer effectively fulfill the role of filtering and removing waste, toxins and fluids from the body. Peritoneal dialysis is characterized by a continuous flux of fluids in and out of the peritoneal cavity. Typically, a patient will undergo four (4) separate "dwell" s of fluid in each 24-hour period. Each dwell draws into the peritoneal cavity waste products and excess fluid from the circulation. On each occasion, the "dirty" fluid is drained out and replaced (i.e., exchanged) with clean fluid. Further, peritoneal dialysis is a patient-managed, daily, chronic and/or long-term treatment. See attached figures at Tab 2.

6. The attached table at Tab 3 illustrates at least some of the distinctions between peritoneal dialysis and the present adhesion reduction technology. Moreover, it should be noted that these technologies are not interchangeable. Medical reasons not to use a peritoneal dialysis solution for adhesion reduction can include the potential of

abdominal bulging, risk of infection when the fluid is not drained, and risk of dehydration as a result of the drawing-in of fluid into the peritoneal cavity from the circulation. Medical reasons not to use an adhesion reduction solution in peritoneal dialysis can include the failure to draw in fluid and/or waste and the unsuitability of the smaller volume associated with the adhesion reduction solution.

7. Attached at Tab 4 is a graph showing a mode of action of the adhesion reduction fluid as a fluid reservoir, which is in stark contrast to the dynamic fluid exchange mechanism of peritoneal dialysis. In particular, the graph shows that the volume of fluid in the peritoneal cavity remained steady for up to 48 hours. Thereafter, the volume declines slowly, with approximately half the administered volume remaining at 96 hours. In contrast, under the same conditions, a glucose peritoneal dialysis solution and a normal saline solution were almost fully absorbed after 24 hours.

8. An aspect of the adhesion reduction technology described in the present application is currently marketed by Baxter Healthcare Corporation as Adept® and was approved by the U.S. Food and Drug Administration (FDA) in 2006. The package insert information for Adept® can be found at Tab 5.

9. As shown in the figure and graphs at Tab 6, Adept® is a clinically effective product shown to reduce the incidence of adhesions after gynecological laparoscopic surgery. In particular, Adept® (icodextrin 4% solution) was shown to reduce post-surgical adhesions after laparoscopic surgery for adhesiolysis in a double-blind, randomized, controlled study.

The test solutions were 4% icodextrin and Lactated Ringer's saline (LRS). Patients received either the icodextrin or the LRS solution in a double-blind, randomized fashion under a study design shown in the figure at Tab 6.

Safety results reveal that 4% icodextrin was found to be a safe and well-tolerated treatment. Patients who received icodextrin experienced no more pain or fluid leakage than the LRS patients. In terms of effectiveness of the two treatments, icodextrin was superior in virtually every parameter measured as shown in the graph at Tab 6 presenting 1st Primary endpoint (ITT)— Success. "Success" was a clinical endpoint defined in consultation with the FDA specifically for this clinical study and was particularly rigorous. This clinical success parameter corresponded to a reduction of at least three (3) or 30% of the number of pre-existing sites with adhesions between initial surgery and the follow-up laparoscopy. In terms of all clinical adhesion research to date, this research with Adept® was the first study to be conducted under double-blind conditions and was the largest study (> 400 patients) of an adhesion reduction device. As shown in the graph presenting 2nd Primary endpoint (ITT)— Reduction in Incidence at Tab 6, icodextrin was superior to LRS in reducing post-surgical adhesions.

In summary, the adhesion reduction technology described in the present application is distinct from the peritoneal dialysis process described in the cited references.

10. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



Elizabeth Peers, MA, PhD

15th May 2007
Date

Elizabeth Peers MA PhD

A dedicated research and development professional with extensive experience. Cross-functional, international background including regulatory affairs, business development, licensing and general management.

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Career history

2005 – 2006 Innovata plc Ruddington, Nottingham

Director of Clinical and Preclinical Development

Key member of the teams that have taken drugs and devices from concept through preclinical and formulation development and clinical trials, resulting in regulatory approval in the EU, USA and other territories.

Responsible for major international clinical programmes (intended arenas: EU accession states, S. Africa, Russia) with undisclosed partner for branded generic inhaled products.

1997 – 2005 ML Laboratories plc Blaby Hall Leicester

Head of R & D

Responsible for a group of project teams delivering results (from clinical and preclinical studies) for regulatory purposes. This included the areas of renal disease, pain, drug delivery, post-surgical adhesions and prostate cancer, for drugs and devices.

ML acquired gene therapy projects (biologics) from COBRA. I undertook a full review and restructured the clinical development programmes, including oncology and surgical indications; I was a champion for a gene therapy orthopaedic product opportunity.

ML was a codevelopment partner for a phosphate binder up to Phase II clinical trials; I was responsible for overall project programme with special responsibility for clinical programme in EU. The US programme was also in development when the project was delivered.

1990 – 1997 Innovata Biomed Ltd St. Albans Herts.

Research and Projects Manager

Responsible for managing projects across functions.

Projects included clinical trials in renal dialysis, pain, oncology, pulmonary disease, AIDS treatment and prevention. There were sensitive issues to address in these areas of serious life-threatening disease.

Delivered a phase III clinical programme in dialysis patients for regulatory approval, achieved 21 months after first-patient-in.

1983 – 1990	Astra Pharmaceuticals Ltd	Kings Langley, Herts
1988-1990	<u>Clinical Projects Manager</u>	– Bricanyl, Pulmicort Turbohalers
1986-1988	<u>Senior Clinical Scientist</u>	– Losec (omeprazole)
1984-1986	<u>Clinical Scientist</u>	- Plendil, Betaloc (felodipine, metoprolol)
1983-1984	<u>Clinical Research Associate</u>	– Pulmicort MDI (budesonide)

I gained increasing managerial responsibility and therapeutic experience with Astra at a key time in the company's development, principally with the blockbuster Losec. I had extensive contact with Scandinavian colleagues, travelling to Sweden and Denmark regularly (Astra was a Swedish company).

Other employment

1979-80 St. Anne's College Oxford: SCONUL trainee
 1977 + 1978 ICI Pharmaceutical Division: holiday jobs in Safety of Medicines
 Saturday job in Dry Cleaners as a teenager.

Key Skills and Competencies

Overseeing the project management of all stages of drug development: I ensure the project teams deliver the company's objectives, and am responsible for their resources, human and financial. Experience of in-house and out-sourced project teams.

Opinion leader, data monitoring and scientific advisory boards.

Quality/Compliance:

Innovata underwent a FDA GCP inspection in November 2005 for the USA pivotal study for the Adept Adhesion Reduction agent; no 483 was issued.

ML had a MHRA GCP audit in June 2005.

These both demonstrate my team's ability to deliver clinical trial processes to the highest regulatory standards.

Communication skills: I present well in oral and written form to customers and clients in the pharmaceutical/medical devices industry, financial, regulatory (FDA) and medical-scientific communities. I ensure that the company delivers its R&D messages effectively and robustly. I am author on over 30 peer-reviewed scientific publications (see appendix) and lead discussions with groups including competitors at presentations at international scientific meetings.

Collaboration/licensing: I have managed the R&D teams where ML has collaborated with both R&D partners and marketing licensees. Involved in negotiations leading to in- and out-licensing including due diligence and opportunity evaluation on an international basis (EU, USA, Japan).

Risk assessment: R & D activities all have risks and benefits, potential or actual and this evaluation is part of my role, both at project-specific and company-wide levels.

Education and Training

Loughborough University Business School 1999 – 2000
Diploma in Business Direction

Imperial College, University of London 1980 – 1983
PhD Physiological Biochemistry
SERC-CASE Award "Characterisation of Opioid Receptors"
(Reckitt & Colman; supervisors Prof E A Barnard + Dr M J Rance)

Newnham College, Cambridge 1976 – 1979
MA Natural Sciences (Pharmacology) class I

Personal Details

Computer literate, full driving and motorcycle licences. Qualifications in French and Italian; acquaintance of spoken German.

Married with 3 children; late convert to skiing; interests in the arts, crafts and physical exercise; travel; Elder of local church; gardening; member of champion local pub cribbage team.

Appendices:

List of Publications
Referees on request

E.M. PEERS – PUBLICATIONS

1. Peers EM, Lyles GA, Callingham BA. The deamination of isoamylamine by monoamine oxidase in mitochondrial preparations from rat liver and heart: a comparison with phenylethylamine. *Biochem Pharmacol* (1980) 29 (8) 1097-1102
2. Peers EM, Rance MJ, Barnard EA, Haynes AS, Smith CF. Photoaffinity probes for opiate receptors. *Life Sci* (1983) 33 (supp 1) 439-42
3. Lai AF, Newman EL, Peers EM, Barnard EA. Sizes of opioid receptor types in rat brain membranes. *Eur J Pharmacol* (1984) 103 (3-4) 349-54
4. Peers E, Shaw JS, Rance MJ, Barnard EA. Specificity of the opioid affinity reagent DALECK in a set of isolated tissue systems. *Neuropeptides* (1986) 8 (4) 317-25
5. Patel KR, Peers E. Felodipine, a new calcium antagonist, modifies exercise induced asthma. *Am Rev Respir Dis* (1988) 138 (1) 54-56
6. Groom P, Simpson RJ, Singh B, Ward DE, Peers E, Richardson PD. A double blind comparison of felodipine and hydrochlorothiazide added to metoprolol to control hypertension. *Eur J Clin Pharmacol* (1988) 34 (1) 21-24
7. Carle WK, Latta D, Lees CT, Lough LR, Pender J, Ross JR, Sefton S, Peers E, Richardson P. A comparison with felodipine and propranolol as additions to hydrochlorothiazide in hypertension. *Euro J Clin Pharmacol* (1988) 34 (2) 115-118
8. Crowe JP, Wilkinson SP, Bate CM, Willoughby CP, Peers EM, Richardson PD. Symptom relief and duodenal ulcer healing with omeprazole or cimetidine. *Aliment Pharmacol Therap* (1989) 3 (1) 83-91
9. Bate CM, Wilkinson SP, Braddy GV, Bateson MC, Hislop WS, Crowe JP, Willoughby CP, Peers EM, Richardson PD. Randomised double blind comparison of omeprazole and cimetidine in the treatment of symptomatic gastric ulcer. *Gut* (1989) 30 (10) 1323-8

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11. Davis RH, Stott NC, Barber JH, Freeling P, Peers EM, Richardson PD. Treatment of peptic ulcer in general practice and in hospital: a comparison of omeprazole and cimetidine
12. Bhatia M, Campbell LM, Ross JR, Taylor MD, Peers EM, Richardson PD
Intranasal budesonide once daily in seasonal allergic rhinitis
Current Med Res Opin (1991) 12 (5) 287-95
13. Stein A, Peers E, Hattersley J, Harris KS, Feehally J, Wall J
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14. Mistry CD, Gokal R, Peers EM
A randomized multicentre clinical trial comparing isosmolar icodextrin with hyperosmolar glucose in CAPD: a 6 month study
Kidney Int (1994) 46 (2) 496-503
15. Gokal R, Mistry CD, Peers EM
Peritonitis occurrence in a multicentre study of icodextrin and glucose in CAPD
Perit Dial Int (1995) 15 (6) 226-30
16. Peers EM, Scrimgeour AC, Haycox AR
Cost-containment in CAPD patients with ultrafiltration failure
Clin Drug Invest (1995) (10) 53-58
17. Posthuma N, ter Wee PM, Donker AJ, Oe PL, Van Dorp W, Peers EM, Verbrugh HA
Serum disaccharides and osmolality in CCPD patients using icodextrin or glucose as daytime dwell
Perit Dial Int (1997) 17 (6) 602-7
18. Posthuma N, ter Wee PM, Verbrugh HA, Oe PL, Peers E, Sayers JA, Donker AJ.
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Nephrol Dial Transplant (1997) 12 (3) 550-3
19. Hindle M, Peers EM, Parry-Billings M, Chrystyn H.
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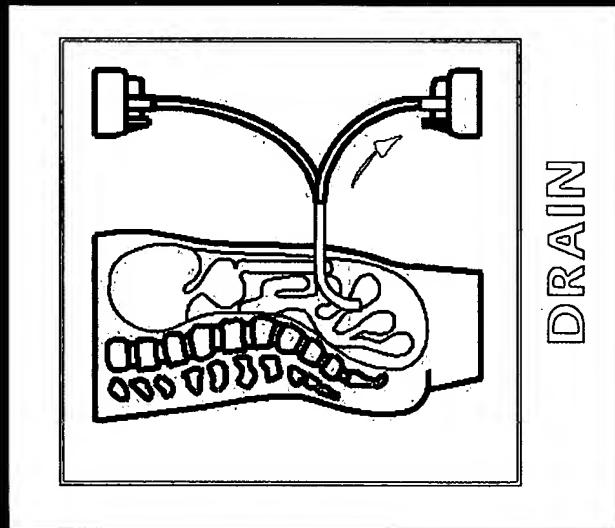
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 Icodextrin use in CCPD patients with peritonitis.
 Nephrol Dial Transplant (1998) 13 (9) 2341-4
 23. Shaunak S, Thornton M, John S, Teo I, Peers E, Mason P, Krausz T, Davies DS.
 Reduction of the viral load of HIV-1 after intraperitoneal administration of dextrin-2-sulphate in patients with AIDS.
 AIDS (1998) 12 (4) 399-409
 24. Morice AH, Waterhouse JC, Peers EM, Parry-Billings M.
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 Respiration (1998) 65 (2) 120-4
 25. Peers E, Gokal R.
 Icodextrin provides long dwell peritoneal dialysis and maintenance of intraperitoneal volume.
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 28. Posthuma N, Verbrugh HA, Donker AJ, van Dorp W, Dekker HA, Peers EM, Oe PL, ter Wee PM.
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 Perit Dial Int (2000) 20 (2) 174-80
 29. Posthuma N, ter Wee PM, Donker AJ, Oe PL, Peers EM, Verbrugh HA.
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 30. Flessner M, Peers E & Rodgers KE
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- model suitability.
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31. Hosie K, Gilbert JA, Kerr D, Brown CB, Peers EM.
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Drug Deliv (2001) 8 (1) 9-12
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A randomized, controlled pilot study of the safety and efficacy of 4% icodextrin solution in the reduction of adhesions following laparoscopic gynaecological surgery.
Hum Reprod (2002) 17 (4) 1031-1038
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35. Peers EM, Chapman A, Brown CB, Rhodes N, Toft A.
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American Fertility Society Score as a measure of the effectiveness of 4% icodextrin in a pivotal adhesion reduction trial in the USA.
J Amer Soc Repro Med (2005) 84 (supp 1) S160 P25.
39. Peers EM Brown CB.
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J Amer Soc Repro Med (2005) 84 (supp 1) S161 P27.

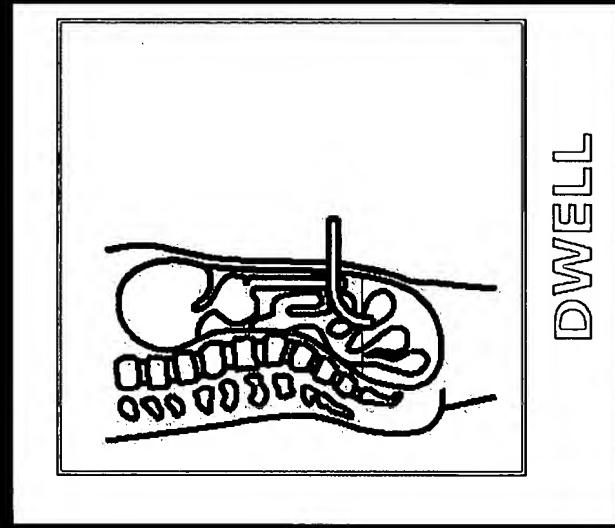
Peritoneal dialysis

- continuous flux of fluid in and out
- each 'dwell' draws in waste products and excess fluid
- 'dirty' fluid drained out, replaced with clean fluid at each 'exchange'
- patient-managed, daily, chronic, long-term use

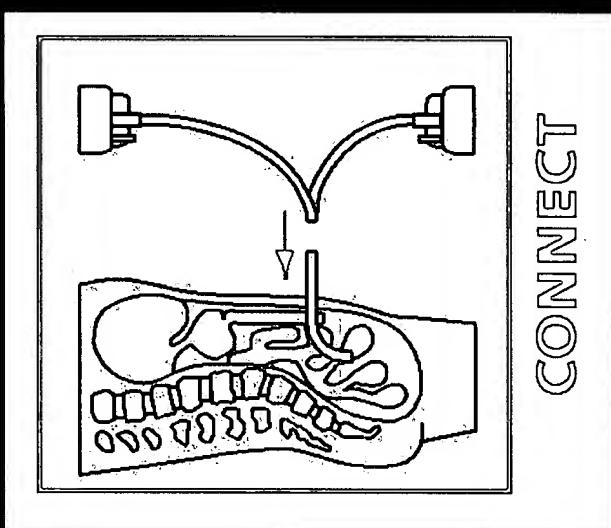
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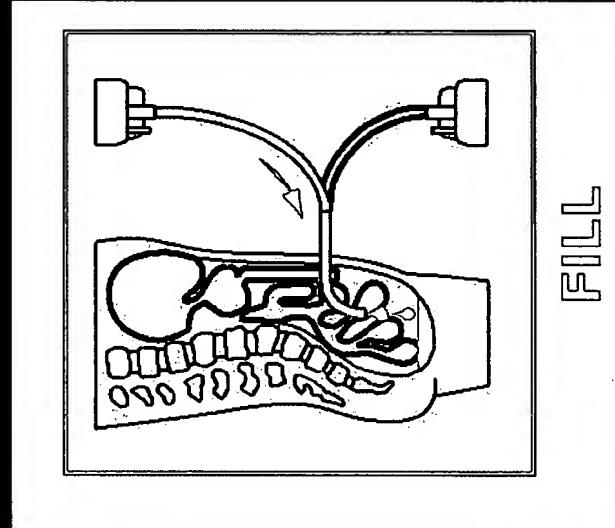
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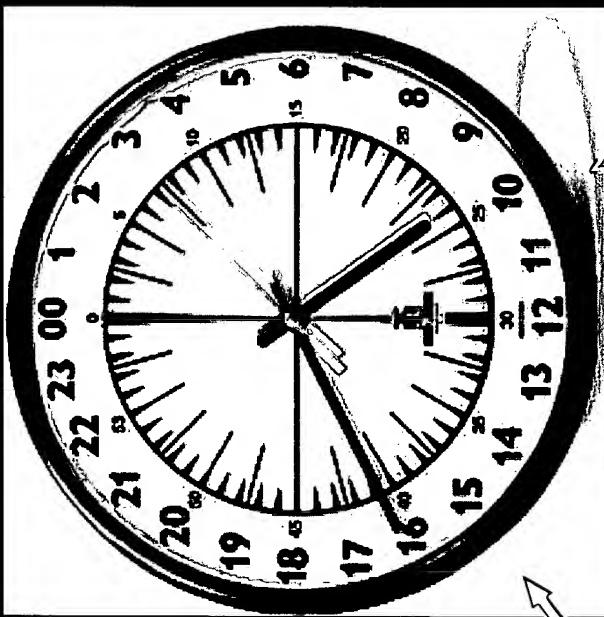
dextrin 'long dwell'
(10h)

exchange (0.5h)

glucose
dwell
(4h)

exchange (0.5h)

glucose dwell
(4h)



exchange (0.5h)

glucose
dwell
(4h)

exchange (0.5h)

Peritoneal Dialysis

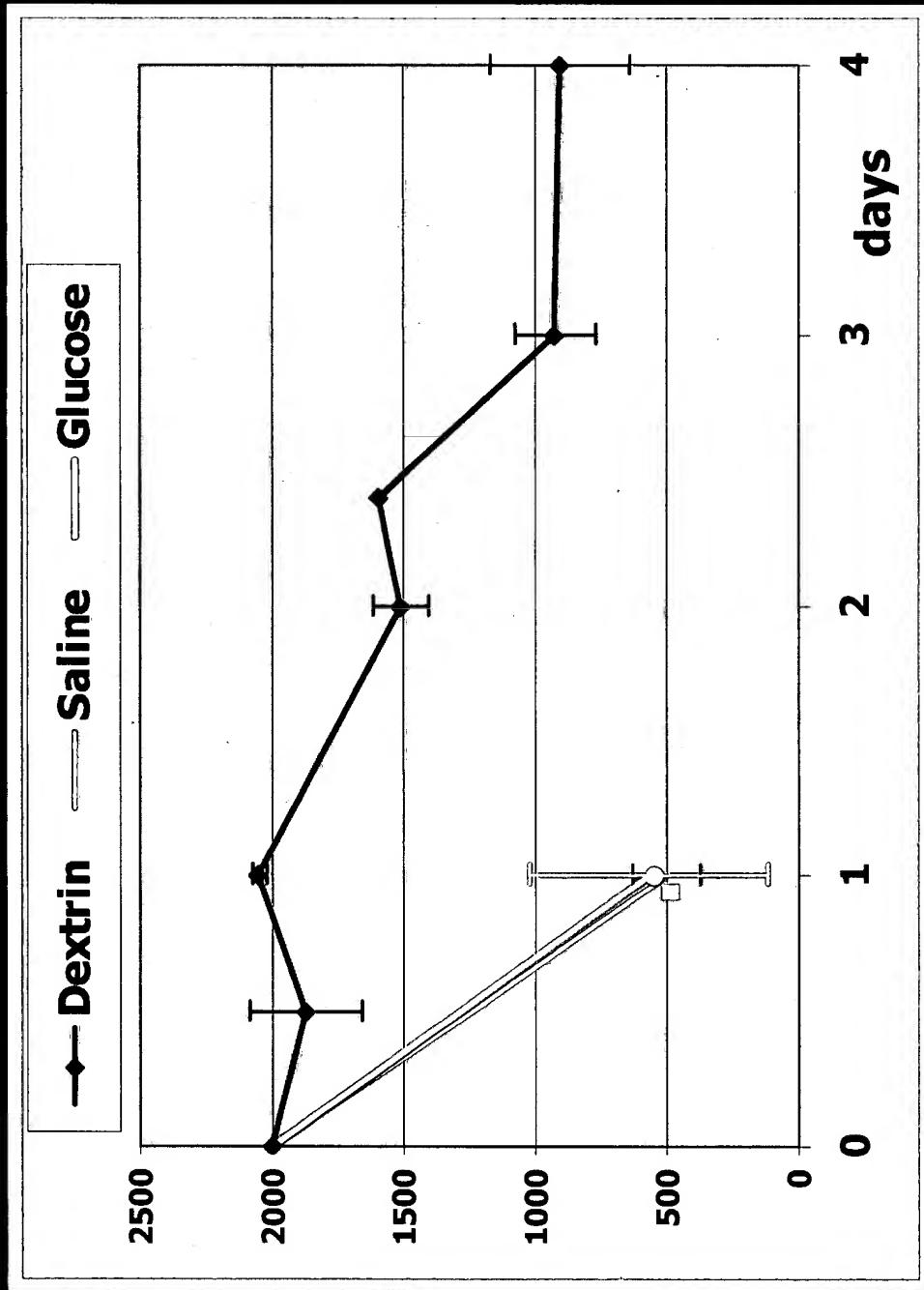


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Fundamentals

Peritoneal dialysis	Adhesion reduction
patient-performed	surgeon-administered in OR
life-long daily treatment	One single treatment
action: fluid and waste disposal	action: reservoir
FDA-approved as a drug	FDA-approved as a device

Mode of action – fluid reservoir



adhesion formation

Hosie et al. Drug Del 2001; 8: 9-12

Strictly Confidential

Baxter**adept®**

Adhesion Reduction Solution (4% Icodextrin)

INFORMATION FOR PRESCRIBERS

CAUTION: FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN.

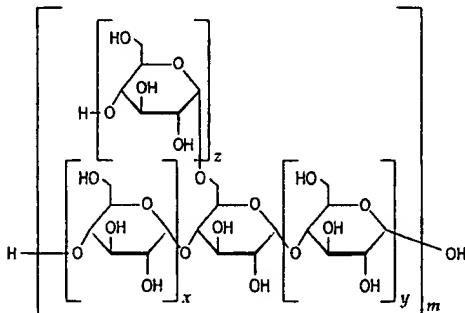
CAUTION: DO NOT USE UNLESS SOLUTION IS CLEAR AND CONTAINER IS UNDAMAGED.

CAUTION: ADEPT® is for direct intraperitoneal administration only.
NOT FOR INTRAVENOUS (IV) ADMINISTRATION.

I. DEVICE DESCRIPTION AND MECHANISM OF ACTION

ADEPT® (4% Icodextrin) Adhesion Reduction Solution is a single use, sterile, clear, colorless-to-pale yellow fluid for intraperitoneal administration containing icodextrin at a concentration of 4% w/v in an electrolyte solution. Icodextrin is a cornstarch-derived, water-soluble branched glucose polymer linked by alpha (1-4) and less than 10% alpha (1-6) glucosidic bonds with a weight-average molecular weight between 13,000 and 19,000 Daltons and a number-average molecular weight between 5,000 and 6,500 Daltons. The representative structural formula of icodextrin is:

Figure 1: Structural Formula of Icodextrin



Each 1 liter of ADEPT® contains:

Icodextrin	40 g
Sodium Chloride	5.4 g
Sodium Lactate	4.5 g
Calcium Chloride	257 mg
Magnesium Chloride	51 mg

Theoretical osmolarity 278 milliosmoles per liter

Ionic composition (approximately) per liter:

Sodium	133 mmol
Calcium	1.75 mmol
Magnesium	0.25 mmol
Chloride	96 mmol
Lactate	40 mmol

ADEPT® is packaged in flexible polyvinylchloride bags containing 1 L or 1.5 L of solution. When stored at temperatures below 30°C ADEPT® has a shelf life of 24 months. ADEPT® should not be refrigerated or frozen.

MECHANISM OF ACTION AND CLEARANCE

Icodextrin, as an alpha (1-4)-linked glucose polymer, is similar in structure to carbohydrates which occur physiologically, e.g. glycogen. When administered intraperitoneally as a 4% solution, icodextrin functions as a colloid osmotic agent. This colloidal osmotic action of icodextrin allows the retention of a reservoir of fluid within the peritoneal cavity for 3-4 days.¹

ADEPT® is believed to perform its function through a physical effect by providing a temporary separation of peritoneal surfaces by hydrofloatation as a result of maintaining a fluid reservoir. This minimizes tissue apposition during the critical period of fibrin formation and mesothelial regeneration following surgery, thereby providing a barrier to adhesion formation.

Pharmacokinetics of Icodextrin

Absorption

Absorption of icodextrin from the peritoneal cavity follows zero-order kinetics, consistent with convective transport via the lymphatic pathways. Studies in patients undergoing continuous ambulatory peritoneal dialysis (CAPD) indicate that a median of 40% of the instilled icodextrin was absorbed from the peritoneal solution during a 12 hour dwell.²

Metabolism and Elimination

When given intraperitoneally, the icodextrin polymer is not metabolized significantly in the peritoneal cavity but is slowly transferred into the systemic circulation by peritoneal lymphatic drainage. In the systemic circulation icodextrin is rapidly metabolized by alpha-amylase to lower molecular weight oligosaccharides, which along with icodextrin, are eliminated by renal excretion. The rate of clearance of icodextrin from the systemic circulation has been estimated to be equal to glomerular filtration rate.

II. INDICATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

INDICATION FOR USE

ADEPT® Adhesion Reduction Solution is indicated for use intraperitoneally as an adjunct to good surgical technique for the reduction of post-surgical adhesions in patients undergoing gynecological laparoscopic adhesiolysis.

CONTRAINDICATIONS

ADEPT® is contraindicated:

- In patients with known or suspected allergy to cornstarch based polymers e.g. icodextrin, or with maltose or isomaltose intolerance, or with glycogen storage disease.
- In the presence of frank infection (e.g. peritonitis) in the abdomino-pelvic cavity.
- In procedures with laparotomy incision. Serious post-operative wound complications including dehiscence and cutaneous fistula formation have been reported from clinical experience outside the US when ADEPT® was used in surgical cases with laparotomy incision.
- In procedures involving bowel resection or repair, or appendectomy. Anastomotic failure, ileus and peritonitis following procedures involving bowel resection and instillation of ADEPT® have been reported from clinical experience outside of the US.

WARNINGS

- There have been rare reports of sterile peritonitis following the use of icodextrin. The differential diagnosis of abdomino-pelvic pain following instillation of ADEPT® should include peritoneal cavity infection, perforated bowel or other viscous, intraperitoneal bleeding, and other life threatening post-operative complications in addition to sterile peritonitis.
- Leaking ADEPT® fluid through laparoscopic port sites post-operatively is associated with wound complications such as subcutaneous fluid collection, skin separation and infection. Meticulous closure of fascia may help reduce wound complications related to fluid extravasation following gynecologic laparoscopy surgery.
- There have been rare reports of hypersensitivity reactions in patients treated with ADEPT®. Anaphylaxis has been reported in a few patients.
- There are rare reports of pulmonary edema, pulmonary effusion and arrhythmia from clinical experience with ADEPT® outside of the US. These cases tended to occur in elderly or otherwise debilitated patients (e.g. cancer patients). The potential benefit of ADEPT® for adhesion prevention should be carefully weighed against the risk of serious complications in patients with serious co-morbidities.
- Foreign body reactions may occur with ADEPT®, as with any implanted material.

PRECAUTIONS

- ADEPT® is for direct intraperitoneal administration only. **NOT** for intravenous (IV) administration.
- ADEPT® is not indicated as a delivery system for intraperitoneal drugs such as antibiotics and chemotherapeutic agents.
- The effectiveness of ADEPT® has not been established for longer term clinical outcomes following gynecological surgery, e.g. pregnancy and pain.
- Self-limited vulvar swelling is a known side-effect of instilling large volumes of fluid into the abdomino-pelvic cavity. Most cases resolve within one week of surgery. When swelling is associated with urinary retention, catheterization may be necessary.
- Maltose metabolites of icodextrin may interfere with blood glucose measurement in diabetic patients who use rapid blood glucose systems that are not glucose specific.

- The safety and effectiveness of ADEPT® have not been evaluated:
 - in patients less than 18 years of age;
 - in pregnancy;
 - when volume left in peritoneal cavity exceeds 1 L;
 - in patients with abnormal liver and/or renal function; or
 - in cases where there is a breach in the vaginal epithelium;

III. ADVERSE EVENTS

Postmarketing Passive Surveillance Outside of US

ADEPT® Adhesion Reduction Solution was approved for use in Europe in October 1999. A Europe-wide multicenter registry for evaluating clinical experience using ADEPT® was launched in 2000. The ARIEL registry was intended to capture the experience of surgeons using ADEPT® in both general and gynecological surgery. Data were collected between September 2000 and December 2003.

A total of 4620 patients were enrolled in the ARIEL registry. Of these, 2882 were gynecology patients (72% laparoscopy) and 1738 were general surgery patients (85% laparotomy). Adverse events were reported in 7.5% gynecological laparoscopy and 13.9% gynecological laparotomy patients compared with 16.7% general surgery laparoscopy and 30.6% general surgery laparotomy patients.^{3,4} Table 1 summarizes key events. These events are presented regardless of the reporting surgeon's causality assessment.

Table 1. Selected Key Adverse Events from ARIEL Registry^a

Adverse Event	Gynecology N=2882			General Surgery N=1738		
	Laparoscopy	Laparotomy	Not known	Laparoscopy	Laparotomy	Not known
Wound complication ^b	13	15	1	2	68	4
Vulvar Swelling	7	1	3	0	1	0
Failed anastomosis	0	0	0	4	33	0
Illeus	3	2	1	4	46	1
Pain	15	10	2	4	9	0
Pulmonary Complication	0	3	0	1	7	0
Allergic Reaction ^c	0	2	0	0	2	0

^a Adverse events in this table were tabulated using a different methodology from that of Sutton³ et al., and Menzies⁴ et al. Therefore, numbers of events in different categories may not correspond exactly with the numbers in the published literature.

^b "Wound complication" includes subcutaneous fluid collection near the incision/port site.

^c Icodextrin has been associated with sldn reactions such as rash. Three of the cases in the above table were more serious events and had systemic involvement.

US Clinical Trial Experience

ADEPT® has been studied in three randomized, controlled US clinical trials involving a total of 548 patients undergoing gynecological laparoscopic surgery with second look laparoscopy 4-12 weeks after the initial procedure. In all three studies, the control device was Lactated Ringer's Solution (LRS). Two pilot studies to obtain preliminary safety data enrolled a total of 99 (59 ADEPT® treated, 40 LRS) patients. The third US clinical trial of ADEPT® was a double-blind pivotal study in which 449 subjects (227 ADEPT® treated, 222 LRS) were treated.

Pilot Studies:

In the first pilot study (CLASSIC), 62 subjects (34 ADEPT® and 28 LRS) were evaluated. Approximately two liters of solution were used for irrigation intraoperatively, and one liter was instilled at the end of the procedure. Two cases of moderate labial or vulvar swelling were reported in the ADEPT® subjects. There were no LRS-related adverse events.

In the second pilot study (RAPIDS), 37 subjects (25 ADEPT® and 12 LRS) were evaluated. Approximately 1500-1900 mL of solution were used for irrigation intraoperatively. An average 2L of ADEPT® vs. 1300mL LRS was instilled at the end of the procedure. The objective of this study was to evaluate the safety of larger volumes of ADEPT® as a post-operative instillate. One case of labial swelling was reported in an ADEPT® subject.

Pivotal Clinical Trial:

In the double-blind, pivotal study, ADEPT® or LRS was used as an intraoperative irrigant (100mL every 30 minutes) and 1L was instilled into the peritoneal cavity at the end of the procedure. 221 (97.4%) ADEPT® patients reported a total of 1065 events compared to 218 (98.2%) LRS patients who reported 1047 events.

Table 2 presents adverse events reported in $\geq 5\%$ of patients (regardless of causality) in the pivotal trial.

Table 2: Pivotal Study Most Frequent Adverse Events (i.e. those reported by at least 5% of patients in either group, regardless of causality) – Intention-to-Treat (ITT) Population

	ADEPT®		LRS	
	Number of patients reporting	Number of reports	Number of patients reporting	Number of reports
Total number of patients at risk	227		222	
Post procedural pain	192 (84.6%)	223	194 (87.4%)	233
Headache	81 (35.7%)	131	72 (32.4%)	127
Nausea	39 (17.2%)	41	37 (16.7%)	41
Leaking from Port Sites Post-procedure	31 (13.7%)	31	30 (13.5%)	30
Dysmenorrhea	30 (13.2%)	32	26 (11.7%)	34
Constipation	24 (10.6%)	26	23 (10.4%)	24
Pelvic pain	23 (10.1%)	32	21 (9.5%)	21
Athralgia	20 (8.8%)	22	19 (8.6%)	19
Flatulence	19 (8.4%)	19	17 (7.7%)	19
Urinary tract infection	16 (7.0%)	17	12 (5.4%)	13
Abdominal pain	15 (6.6%)	26	19 (8.6%)	23
Dysuria	15 (6.6%)	16	8 (3.6%)	9
Nasopharyngitis	15 (6.6%)	15	18 (8.1%)	18
Vaginal bleeding	14 (6.2%)	15	5 (2.3%)	5
Abdominal distension	13 (5.7%)	13	10 (4.5%)	10
Post procedural nausea	13 (5.7%)	13	20 (9.0%)	20
Pyrexia	13 (5.7%)	13	7 (3.2%)	7
Vomiting	13 (5.7%)	13	22 (9.9%)	22
Labial, Vulvar or Vaginal swelling	13 (5.7%)	13	1 (0.45%)	1
Back pain	12 (5.3%)	15	12 (5.4%)	13
Insomnia	12 (5.3%)	14	8 (3.6%)	8
Cough	10 (4.4%)	10	12 (5.4%)	13
Diarrhea	3 (1.3%)	3	13 (5.9%)	15

In the pivotal study, the most frequently occurring (report incidence as % of number of patients) treatment-related adverse events between surgeries were post procedural leaking from port sites, labial, vulvar or vaginal swelling and abdominal distension.

IV. CLINICAL STUDIES

ADEPT® has been studied in the USA in two pilot studies and one double-blind, pivotal study in female patients undergoing gynecological laparoscopic surgery with a planned second look laparoscopy. The studies were conducted to evaluate the safety and effectiveness of the device as an adjunct to good surgical technique in the reduction of post-surgical adhesions in comparison to (LRS). ADEPT® or LRS was used as an intra-operative irrigant (100 mL every 30 minutes) in all studies; in the pivotal study, 1L of ADEPT® or LRS was instilled into the peritoneal cavity at the end of the surgical procedure. In the pilot studies, 1L in the first study and up to 2L in the second study were instilled at the end of surgery. In all three studies, the incidence, extent and severity of adhesions were assessed at 23 prospectively determined anatomical sites, using established adhesion scoring methods at baseline surgery (prior to adhesiolysis) and at second look laparoscopy. Safety was evaluated based on adverse events and clinical laboratory tests.

For both pilot studies, second look laparoscopy took place 6-12 weeks after the initial surgery. In both of these studies, there was a greater reduction in the number of sites with adhesions, and the extent and severity of adhesions in the ADEPT® subjects compared to the LRS subjects. However, these differences were not statistically significant, which may be due in part to the relatively small numbers of subjects in these studies.

PIVOTAL STUDY

The pivotal study was a comparative, double-blind, randomized, multicenter study in the USA. A total of 449 female patients aged eighteen or over were enrolled for whom laparoscopic peritoneal cavity surgery was planned for a gynecological procedure which included adhesiolysis and who agreed to undergo second look laparoscopy as part of their treatment plan at 4-8 weeks after the initial surgery. The patients had to have adhesions at three or more of the 23 pre-specified anatomical sites and adhesions at three or more of the anatomical sites had to be lysed during the surgery.

Objectives

The study objectives were to determine the effectiveness and safety of ADEPT® when used as an intraoperative washing solution with a postoperative instillate in the reduction of post-surgical adhesions after laparoscopic surgery for adhesiolysis, compared with LRS.

Inclusion Criteria:

- willing, able to and having freely given written consent to participate in the study and abide by its requirements;
- female patients aged eighteen and over, in good general health including ASA (American Society of Anesthesiologists) score of 2 or less;

- laparoscopic peritoneal cavity surgery is planned for a gynecologic procedure which includes adhesiolysis; and
- patient agrees to planned second look laparoscopy for this study 4-8 weeks after the initial surgical procedure.

Exclusion Criteria (pre-operative):

- current pregnancy including ectopic pregnancy;
- SGOT, SGPT and/or bilirubin > 20% above the upper range of normal and considered clinically significant;
- BUN and creatinine > 30% above the upper range of normal and considered clinically significant;
- concurrent use of systemic corticosteroids, antineoplastic agents and/or radiation;
- active pelvic or abdominal infection;
- known allergy to starch-based polymers; and
- additional surgical procedure (non-OB/GYN) planned to be performed during the laparoscopic procedure.

Exclusion Criteria (intra-operative):

- clinical evidence of cancer;
- clinical evidence of pregnancy including ectopic pregnancy;
- use during this procedure of any approved or unapproved product for the purpose of preventing adhesion formation;
- fewer than 3 of the available anatomical study sites contain adhesions;
- less than three of the anatomical sites are lysed;
- if the procedure needs to be performed by a laparotomy (decision made after laparoscopy has commenced);
- if any of the anatomical sites being scored for the purposes of this study are being removed during surgery;
- if all of the available anatomical sites cannot be visualized and recorded on the video tape during the surgery; and
- any unplanned surgery which involves opening of the bowel (excluding appendectomy).

Study Hypotheses

There were three co-primary outcome measures, each with a respective hypothesis:

- (1) The first co-primary endpoint for the pivotal study was the difference (for an individual study subject) in the number of adhesion sites between baseline and second look laparoscopy. For subjects with ten or fewer adhesions lysed at surgery, an individual patient success was defined as a decrease of at least 3 sites with adhesions between baseline and second look laparoscopy. For subjects with more than ten adhesions lysed at baseline, individual patient success was defined as a decrease in adhesion sites of at least 30% between baseline and second look laparoscopy. The study hypothesis for the first co-primary endpoint was that the lower bound of the 95.2% CI around the difference in success rates will be above 5%.
- (2) The second co-primary endpoint was the difference (for an individual study subject) in the number of adhesion sites between baseline and second look laparoscopy. In the hypothesis for this endpoint, patients served as their own control. The study hypothesis for the 2nd co-primary endpoint was that ADEPT® treated subjects would have fewer sites with adhesions at second look laparoscopy than they had at baseline.
- (3) The third co-primary endpoint was the difference (for an individual subject) in the number of dense adhesion sites between baseline and second look laparoscopy. For the 3rd co-primary endpoint, success for a subject was defined as any reduction in dense adhesion sites between baseline and second look laparoscopy. The study hypothesis for the 3rd co-primary endpoint was that the success rate for ADEPT®-treated subjects would be greater than that for LRS treated subjects.

Secondary Endpoints

The study had the following pre-specified secondary endpoints.

No hypothesis tests were specified for these endpoints.

- Incidence of sites with adhesions
- Severity of sites with adhesions
- Extent of sites with adhesions
- American Fertility Society (AFS) score
- Modified AFS score
- Reformed adhesions
- De novo* adhesions
- Abdominal wall adhesions
- Visceral adhesions
- Visual Analog Scale (VAS) score for pelvic pain

Figure 2 is a patient accounting of all subjects in the pivotal study, including the initial screen.

Figure 2: Patient Accounting

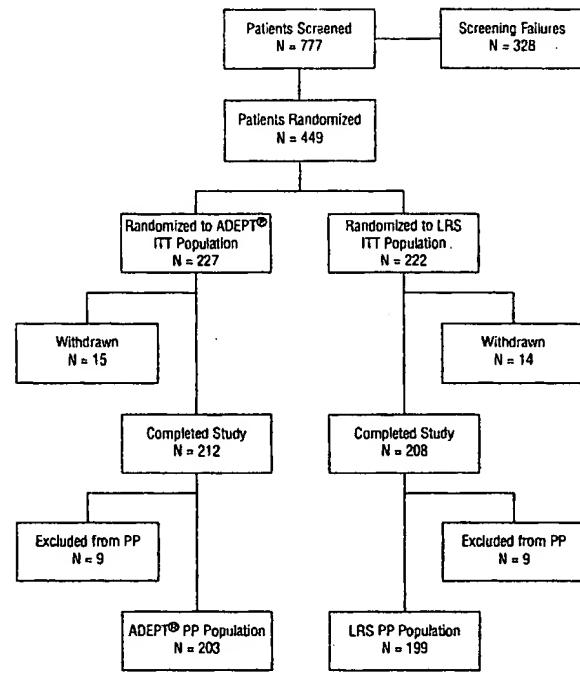


Table 3: Pivotal Study Demographics and Baseline Data, ITT

	ADEPT®	LRS
No. of patients randomized (ITT)	227	222
Demographics ± s.d.		
Age, yr	32.6 ± 5.9	32.3 ± 5.7
Height, in (n)	64.7 ± 2.7 (225)	64.2 ± 2.8 (221)
Weight, lb (n)	153.2 ± 36.9 (225)	152.0 ± 35.0 (220)
Race		
Caucasian	160 (70.5%)	144 (64.9%)
n (%):		
East Asian	3 (1.3%)	7 (3.2%)
African American	32 (14.1%)	32 (14.4%)
Hispanic	24 (10.6%)	35 (15.8%)
Oriental	3 (1.3%)	1 (0.5%)
Other	5 (2.2%)	3 (1.4%)
Base vital signs		
Systolic blood pressure, mmHg (n)	114.9 ± 12.1 (224)	114.5 ± 11.8 (221)
Diastolic blood pressure, mmHg (n)	71.5 ± 8.8 (224)	71.4 ± 8.8 (221)
Heart rate, bpm (n)	73.1 ± 8.8 (224)	73.2 ± 8.3 (218)
Primary diagnosis n (%)		
Pelvic pain	152 (67.0%)	134 (60.4%)
Endometriosis	94 (41.4%)	93 (41.9%)
Infertility	115 (50.7%)	127 (57.2%)
Adhesions	126 (55.5%)	127 (57.2%)
Others	36 (15.9%)	43 (19.4%)
Medical history n (%)		
No. of patients with resolved medical conditions	192 (84.6%)	191 (86.0%)
No. of patients with ongoing medical conditions	224 (98.7%)	219 (98.6%)
No. of patients with surgical history	205 (90.3%)	196 (88.3%)
Baseline assessment of adhesions		
Number of Sites with Adhesions	10.27 ± 4.26	10.34 ± 4.39
Number of Sites with lysed Adhesions	8.69 ± 4.15	8.46 ± 4.02
Number of Sites with dense Adhesions	6.17 ± 4.74	6.23 ± 5.26
Number of Sites with lysed dense Adhesions	5.35 ± 4.56	5.15 ± 4.46
Baseline AFS score for infertility subgroup (PP)	9.52 ± 10.39	8.60 ± 9.99
Baseline mAFS score (PP)	2.71 ± 2.47	2.81 ± 2.93
Endometriosis n (%)		
Present at baseline	140 (61.7%)	135 (60.6%)
Treated	138 (60.8%)	135 (60.8%)
Others		
Operative Time (mins) (median) (ITT)	85.0	88.0
Days between first and second look surgery (ITT)	39.9 ± 10.3	39.9 ± 10.7
Average volume of solution lavaged and instilled, ml (min-max)	3,502	3,570
	(1,300-12,000)	(1,300-12,000)

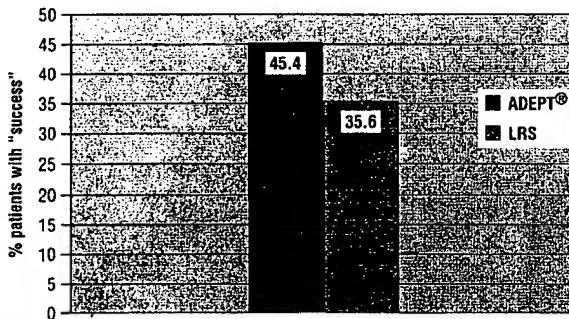
Table 3 shows that the study arms were well balanced. Almost all sites with adhesions were lysed (on average 10 at baseline with 9 lysed for both groups). Similarly, almost all sites with dense adhesions were lysed (on average 6 at baseline and 5 lysed). The study population had a fairly substantial adhesion burden with an average of 10 sites per subject and 6 sites with dense adhesions per subject.

Pivotal Study Results

Primary Effectiveness Endpoints

First Co-Primary Endpoint: 45.4% of the patients in the ADEPT® group were defined as a "clinical success" compared to 35.6% in the LRS group ($p=0.016$, two-tailed test) (Table 4). However, the lower bound of the 95.2% CI around the difference in success rates (0.7%) is below the pre-specified 5% target. Data is presented as intent-to-treat (ITT). (see Figure 3.)

Figure 3: Pivotal Study First primary effectiveness endpoint (percentage of patients achieving "success") – Intention to Treat population



Second Co-Primary Endpoint: Patients in the ADEPT® group had significantly fewer sites with adhesions at second look compared to first look laparoscopy ($p<0.001$). The 95.2% confidence intervals were less than zero for both the ADEPT® treated patients (-2.83 to -1.62) and the LRS-treated patients (-2.24 to -0.96). There was a significantly greater reduction in the number of sites with adhesions in the ADEPT® treated patients compared with the LRS group ($p=0.047$, two-tailed test).

Third Co-Primary Endpoint: In the ADEPT® group, 50% of patients had fewer sites with dense adhesions at second look (mean reduction 1.19 ± 3.43 , $p<0.001$); in the LRS group, the figure was similar (49%) (see Table 4). There was no statistically significant difference between treatments ($p=0.73$).

Table 4: Pivotal Study Primary Effectiveness Endpoints – Intention-to-Treat population

First primary effectiveness endpoint

	ADEPT®	LRS
Total number of patients	227	222
Success ^a	103 (45.4%)	79 (35.6%)
Number reporting		
Difference in % of patients with success	9.8	
Se	4.6	
95.2 CI for % of patients with success	(0.7, 18.9)	
Odds ratio ^b	1.64	
95.2% CI for odds ratio	(1.09, 2.46)	
p-value for treatment	0.016*	

a Success was achieved if the number of sites with adhesions decreased by at least the larger of three sites or 30% of the number of sites lysed

b Estimated from a logistic regression model with factors for treatment group and center. A value >1 favors ADEPT®. The odds ratio (95.2% CI) using exact methods was 1.61 (1.06, 2.46).

* Statistically significant at the 4.8% level, two-tailed

Second primary effectiveness endpoint

	ADEPT®	LRS
Total number of patients	227	222
Number of sites with adhesions		
First look (mean \pm sd)	10.27 \pm 4.26	10.34 \pm 4.39
Second look (mean \pm sd)	7.88 \pm 4.64	8.49 \pm 4.98
Change from first to second look (mean \pm sd)	-2.40 \pm 3.66	-1.86 \pm 3.35
LS mean for change ^a (95.2% CI)	-2.22 (-2.83, -1.62)	-1.60 (-2.24, -0.96)
p-value for change	<0.001***	<0.001***
Difference between LS means ^b	-0.62	
Se	0.31	
95.2% CI	(-1.24, -0.004)	
p-value for treatment	0.047	

a Estimated from an ANCOVA model with factors for treatment group and center and a covariate for first look score

b A negative difference favors ADEPT®

***Statistically significant at the 0.1% level

Third primary effectiveness endpoint

	ADEPT®	LRS
Total number of patients	227	222
Number of sites with dense adhesions		
First look (mean \pm sd)	6.17 \pm 4.74	6.23 \pm 5.26
Second look (mean \pm sd) (n)	5.02 \pm 4.60 (212)	5.25 \pm 5.26 (208)
Change from first to second look (mean \pm sd) (n)	-1.19 \pm 3.43 (212)	-1.01 \pm 3.24 (208)
p-value for change	<0.001	<0.001
Number of patients with fewer dense adhesions at second look	114 (50.2%)	109 (49.1%)
Odds ratio ^a	1.07	
95.2% CI for odds ratio	(0.72, 1.59)	
p-value for treatment	0.73	

a Estimated from a logistic regression model with factors for treatment group and center. A value >1 favors ADEPT®. The odds ratio (95.2% CI) using exact methods was 1.07 (0.71, 1.61).

Secondary effectiveness (per protocol population)

In all (10) secondary effectiveness variables, use of ADEPT® appeared to provide benefits beyond those provided by control, although not all to a statistically significant level. Both groups showed a reduction in adhesion burden, but this was consistently greater in the ADEPT® group.

These secondary endpoints provide supportive evidence for the primary endpoints and have not been adjusted for multiplicity (see Tables 5 to 8). When a multiplicity adjustment is applied to the data, one secondary endpoint remains statistically significant in favor of ADEPT®: the subgroup of patients presenting with a primary diagnosis of infertility showed a statistically significant reduction in AFS score compared to control ($p<0.05$).

Table 5 : Pivotal Study Secondary Effectiveness Endpoints (PP) for Adhesions at Anatomical Sites

Endpoint / Variable	ADEPT® (n=203)	LRS (n=199)	p-value*
Incidence of sites with adhesions			
Change from 1st to 2nd look (mean \pm s.d.)	-2.64 \pm 3.66	-2.02 \pm 3.19	0.039
% patients with reduction	76.4%	69.3%	0.121
Change from 1st to 2nd look excluding non-tysed sites (mean \pm s.d.)	-2.64 \pm 3.66	-2.02 \pm 3.19	0.068
% patients with four or fewer sites with adhesions at 2nd look	32.0	28.1	0.510
Shift analysis - % patients with 2nd look incidence grouped into 4 categories	0: 4.9 1-4: 27.1 5-9: 36.0 ≥10: 32.0	0: 4.5 1-4: 23.6 5-9: 31.7 ≥10: 40.2	0.173
Severity of sites with adhesions			
% change from 1st to 2nd look per patient (mean \pm s.d.)	-24.2 \pm 45.2	-21.5 \pm 41.0	0.415
% patients with reduction	72.9%	69.8%	0.446
Extent of sites with adhesions			
% change from 1st to 2nd look per patient (mean \pm s.d.)	-26.9 \pm 51.4	-21.8 \pm 48.5	0.240
% patients with reduction	77.3%	69.8%	0.084
Modified AFS score			
Change from 1st to 2nd look (mean \pm s.d.)	-0.67 \pm 1.54	-0.48 \pm 1.61	0.094
% patients with reduction	70.4%	69.8%	0.722

* not adjusted for multiplicity.

Table 6: Pivotal Study Secondary Effectiveness Endpoints (PP) for Subgroup of Patients with a Primary Diagnosis of Infertility

Endpoint / Variable	ADEPT® (n=102)	LRS (n=112)	p-value*
AFS score			
Change from 1st to 2nd look for patients with a primary diagnosis of infertility (mean \pm s.d.)	-3.46 \pm 6.77	-1.10 \pm 6.36	0.011
% patients with reduction for patients with a primary diagnosis of infertility	52.9%	30.4%	0.001
Shift analysis - % patients with 2nd look scores grouped into 4 categories for patients with a primary diagnosis of infertility	minimal: 68.6 mild: 10.8 moderate: 11.8 severe: 8.8	minimal: 59.8 mild: 13.4 moderate: 15.2 severe: 11.6	0.041

* not adjusted for multiplicity.

Table 7: Pivotal Study Secondary Effectiveness Endpoints (PP) for Types of and Location of Adhesions

Endpoint / Variable	ADEPT® (n=203)	LRS (n=199)	p-value*
Reformed adhesions			
Number of sites with reformed adhesions (mean \pm s.d.)	4.92 \pm 3.91	5.11 \pm 4.12	0.722
Number of sites without reformed adhesions (mean \pm s.d.)	3.77 \pm 2.72	3.32 \pm 2.29	0.065
% patients with at least one	87.7%	86.9%	0.832
De novo adhesions			
Number of sites with at least one <i>de novo</i> adhesion (mean \pm s.d.)	1.13 \pm 1.85	1.29 \pm 1.61	0.036
% patients free of <i>de novo</i> adhesions	52.7%	42.7%	0.029
Abdominal wall adhesions			
Change from 1st to 2nd look in number of sites (mean \pm s.d.)	-1.17 \pm 1.63	-0.94 \pm 1.60	0.184
% patients with reduction from 1st to 2nd look in no. sites	65.5%	58.3%	0.129
Visceral adhesions			
Change from 1st to 2nd look in number of sites (mean \pm s.d.)	-1.47 \pm 2.62	-1.07 \pm 2.22	0.046
% patients with reduction from 1st to 2nd look in no. sites	68.5%	63.3%	0.228

* not adjusted for multiplicity.

Table 8: Pivotal Study Secondary Effectiveness Endpoints (PP) for Subgroup of Patients with a Primary Diagnosis of Pelvic Pain

Endpoint / Variable	ADEPT® (n=116)	LRS (n=108)	p-value*
VAS score for pelvic pain			
Change from screening to 2nd look for patients with a primary diagnosis of pelvic pain (mean \pm s.d.)	35.8 \pm 32.8	30.8 \pm 30.2	0.995

* not adjusted for multiplicity.

V. DIRECTIONS FOR USE

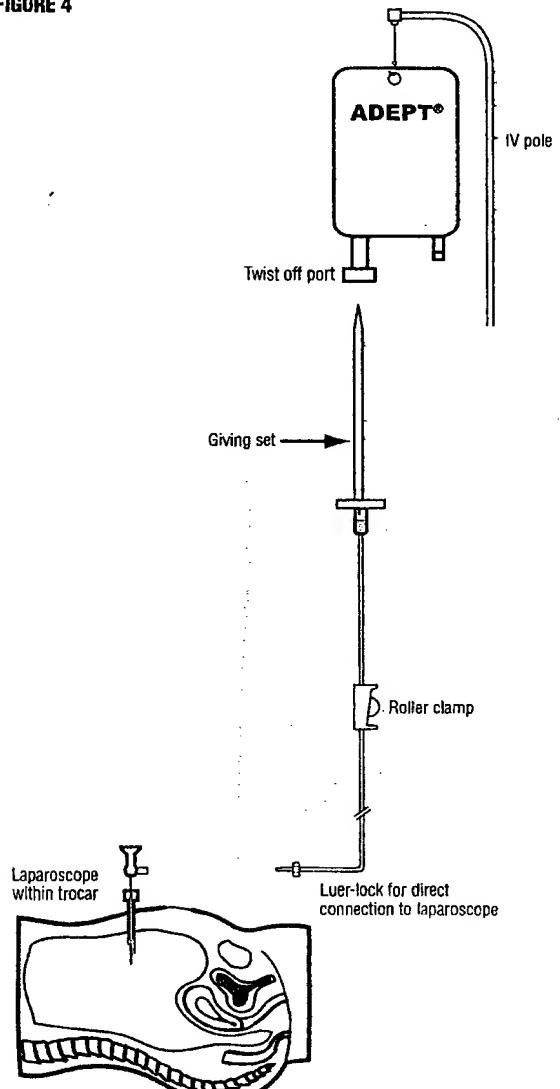
ADEPT® is administered directly into the peritoneal cavity during laparoscopic gynecological surgery, being used as an irrigant solution during the course of surgery. Once the surgeon has completed the surgical procedure(s), the cavity is aspirated of all remaining fluid. A final volume of 1 liter of ADEPT® is then introduced into the cavity before removal of the scope.

Using standard operating room technique:

1. ADEPT® should be warmed to approximately body temperature prior to use, using a device specifically intended for warming solutions in operating rooms.
2. Remove the outer wrap from the ADEPT® bag and hang the sterile bag of solution on an I.V. pole.
3. Remove the twist-off tab from the spike port and insert a giving set for connection to a laparoscope.
4. ADEPT® should be used intra-operatively as an irrigant solution, and as a post-operative instillate. The solution will flow through a giving set and through laparoscopes.
5. When used as an intra-operative irrigant solution, at least 100 mL of ADEPT® should be introduced to the cavity every 30 minutes.
6. Remove remaining fluid before introducing the final instillation.
7. For the final instillation of ADEPT®, prior to removal of the laparoscope, one liter (a new bag of ADEPT® if 1 liter bags are being used) should be used. Direct the solution at the operative sites in the first instance, the remainder being distributed throughout the cavity.
8. Dispose of the bag and any unused portion of the solution following normal operating room biological hazard procedures.

SEE FIGURE 4

FIGURE 4



HOW SUPPLIED

ADEPT® is packaged in single use, flexible polyvinylchloride bags, fitted with connecting ports, containing 1 liter or 1.5 liters of solution. The product is presented sterile (by heating in an autoclave). The bags are packaged in cartons of 10 x 1 liter or 5 x 1.5 liters.

STORAGE

ADEPT® should not be stored above 30°C. Do not refrigerate or freeze.

ADEPT® may be kept in a warming device for up to 14 days, provided it is not removed and then replaced back in the warming device. At all other times, storage below 4°C or above 30°C is not recommended.

References:

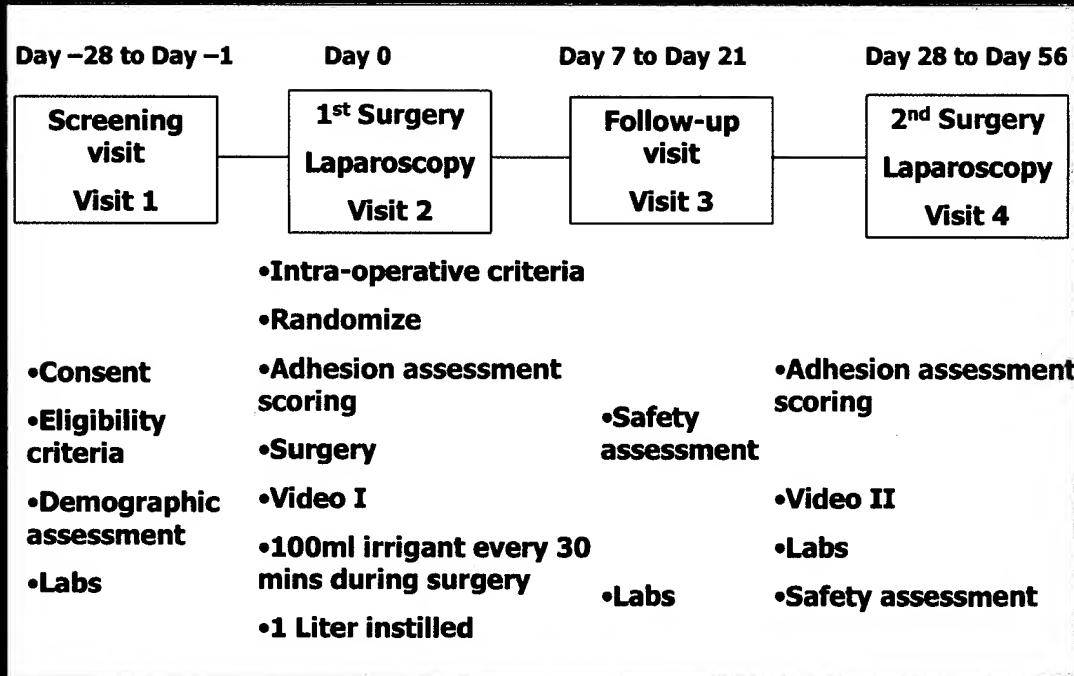
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Deerfield, IL 60015 USA

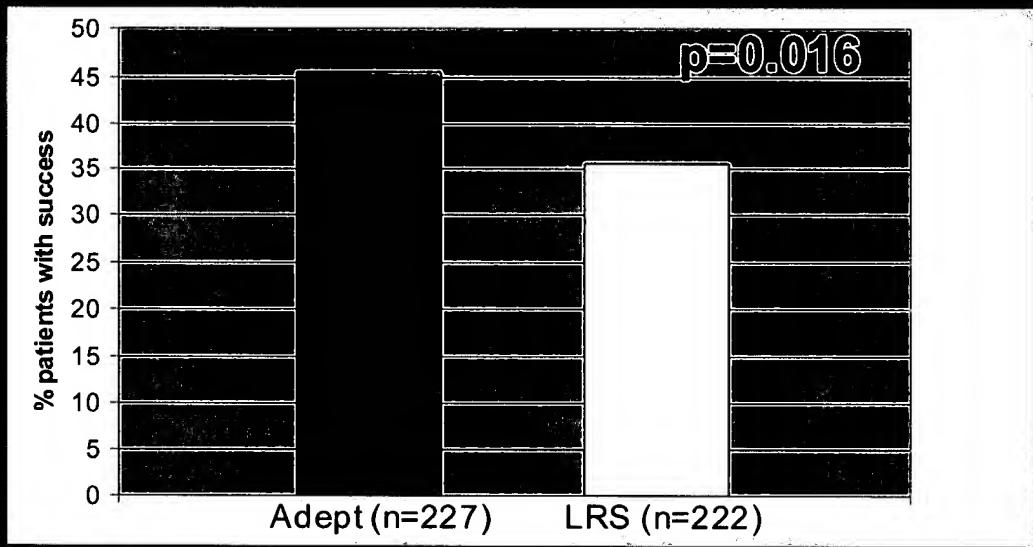
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Study Design



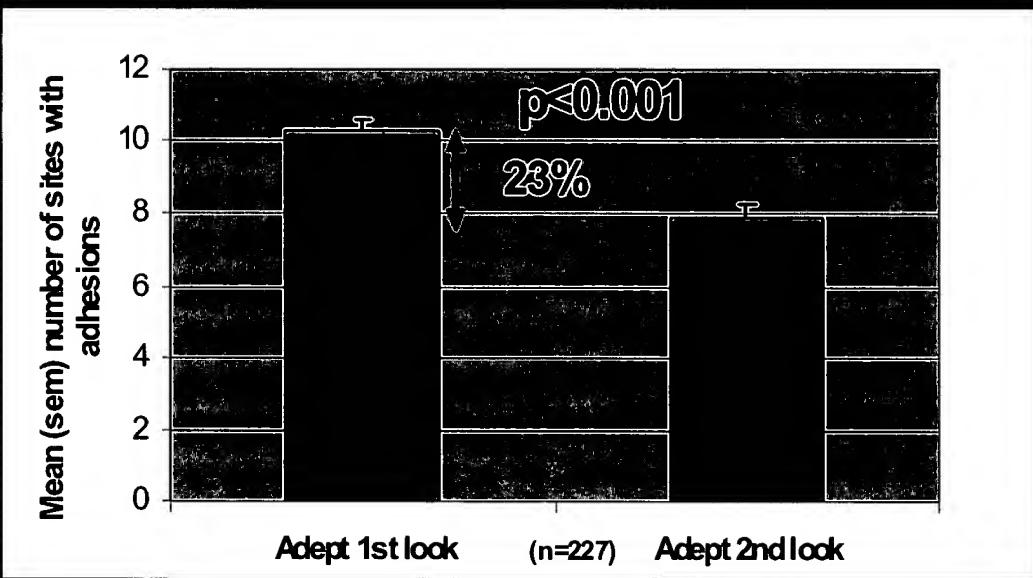
1st Primary endpoint (ITT)

Success



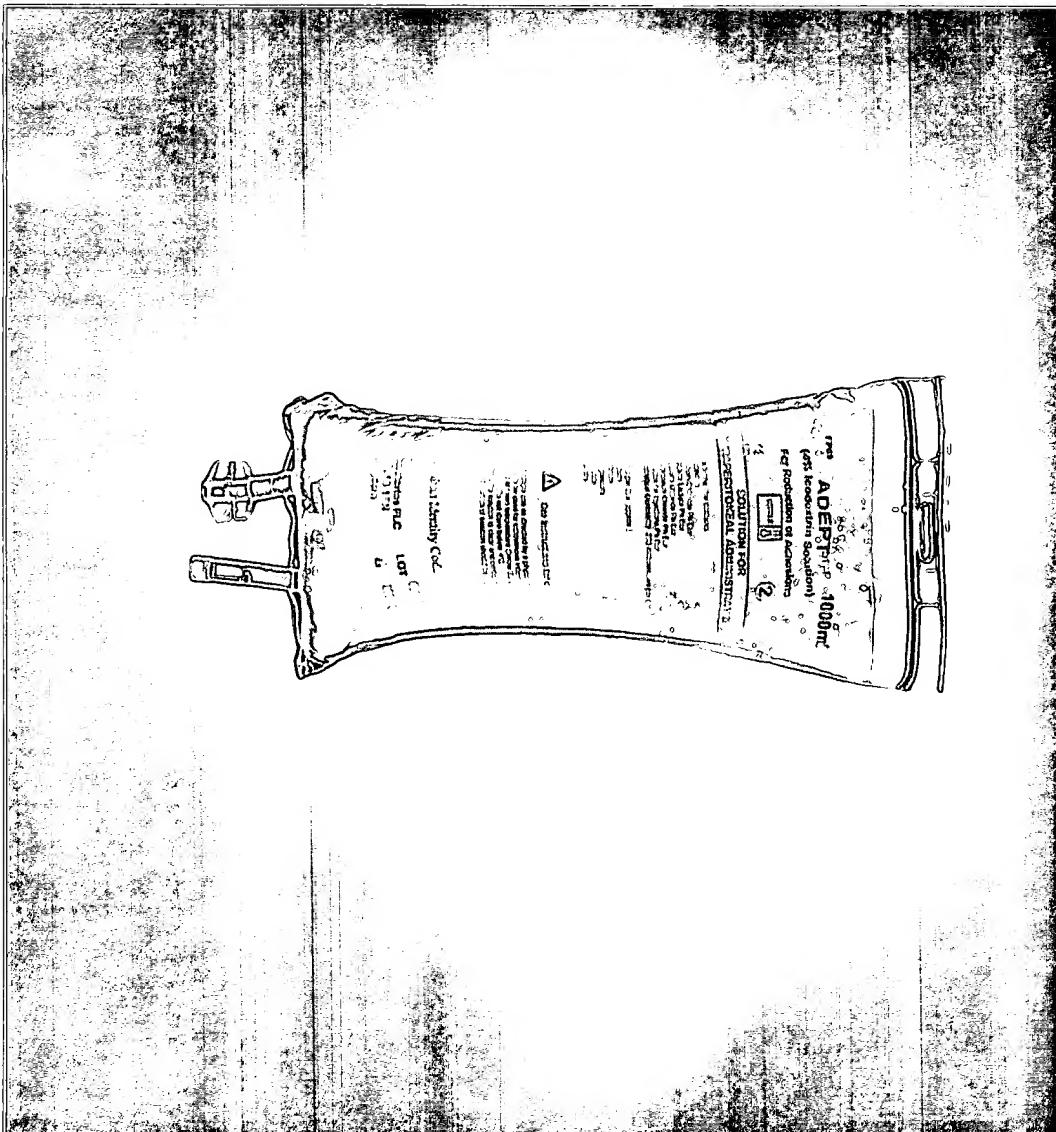
2nd Primary endpoint (ITT)

Reduction in Incidence



Conclusion

- Clinically effective
- A problem solved



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